Review

Bioavailability as an issue in risk assessment and management of food cadmium: A review

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ABSTRACT

The bioavailability of cadmium (Cd) from food is an important determinant of the potential risk of this toxic element. This review summarizes the effects of marginal deficiencies of the essential nutrients zinc (Zn), iron (Fe), and calcium (Ca) on the enhancement of absorption and organ accumulation and retention of dietary Cd in laboratory animals. These marginal deficiencies enhanced Cd absorption as much as ten-fold from diets containing low Cd concentrations similar to that consumed by some human populations, indicating that people who are nutritionally marginal with respect to Zn, Fe, and Ca are at higher risk of Cd disease than those who are nutritionally adequate. Results from these studies also suggest that the bioavailability of Cd is different for different food sources. This has implications for the design of food safety rules for Cd in that if the dietary source plays such a significant role in the risk of Cd, then different foods would require different Cd limits. Lastly, the importance of food-level exposures of Cd and other potentially toxic elements in the study of risk assessment are emphasized. Most foods contain low concentrations of Cd that are poorly absorbed, and it is neither relevant nor practical to use toxic doses of Cd in experimental diets to study food Cd risks. A more comprehensive understanding of the biochemistry involved in the bioavailability of Cd from foods would help resolve food safety questions and provide the support for a badly needed advance in international policies regarding Cd in crops and foods.

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1.   Introduction

In the context of this paper, bioavailability is defined as the degree to which a nutrient, toxin, or other substances become available for body use or deposition after exposure. When exposure to the substance is oral, bioavailability generally includes absorption, body utilization, and/or deposition. Cadmium (Cd) is generally considered a toxic element where food is the major source of acquisition. Up to a point, intestinal absorption of Cd is proportional to the concentration in the diet, and in the past, the amount of the element in food has been regarded as the overriding risk factor that determines the body burden of Cd. However, other factors influence the rate of intestinal absorption and organ retention of Cd.

Perhaps the most important factor in this regard is the interaction between Cd and other mineral nutrients that are antagonistic to Cd absorption. The rate of Cd absorption from various food sources is reduced if the nutritional status of zinc (Zn), iron (Fe) or calcium (Ca) of the individual is high (Evans et al., 1970; Kello and Kostial, 1977; Koo et al., 1978; Fox et al., 1979; Jacobs et al., 1983; Fox, 1983; Fox, 1988; Ferguson et al., 1990; Brzóska and Moniuszko-Jakoniuk, 1998). However, if the general nutritional status of these minerals in the consumer is low, then Cd absorption will be enhanced. Flanagan et al. (1978) were among the first to show that Fe deficiency caused an increase in Cd absorption in both mice and humans. More recent work has shown that marginal dietary deficiencies of Fe, Zn, and Ca also have a strong effect on the bioavailability of Cd from food (Reeves and Chaney, 2001; Reeves and Chaney, 2002; Reeves and Chaney, 2004; Reeves et al., 2005). The following is a review of this work and a discussion of how these findings might influence risk assessment and management of food cadmium.

2.   Research outcomes

A recent series of experiments evaluated the effects of marginal dietary intakes of Zn, Fe, and/or Ca and their interactions on Cd absorption and its accumulation and retention in various organs (Reeves and Chaney, 2001; Reeves and Chaney, 2002; Reeves and Chaney, 2004; Reeves et al., 2005). The term "marginal" was defined as that concentration of dietary Zn, Fe, or Ca that is less than the requirement for the rat as defined by the U.S. National Research Council (NRC) (1995), but not low enough to initiate frank signs of deficiencies such as reduced weight gain. The general study design was to use food-based diets made with sunflower kernel (SFK) or rice containing concentrations of Cd that are found naturally — 0.25–0.45 mg Cd/kg. In addition, the diets contained adequate Zn, Fe, and/or Ca as defined by the National Research Council, or marginal concentrations amounting to approximately 70, 30, and 50% of the respective adequate concentrations. The SFK (0.6–0.8 mg Cd/kg) were roasted, ground, and incorporated into the diet at 20%. Rice was cooked with Cd in the water, dried (0.6 mg Cd/kg), and incorporated into the diet at 40%. Please note that these foods were formulated into the diets to account for their inherent nutrient content. Rats were fed their respective diets for five weeks and then given a 1.0 g-meal labeled with ^{109}Cd.

The amount of label retained in the body was monitored by whole-body-counting for up to 16 days. Absorption was calculated according to the procedure outlined by Reeves and Chaney (2001, 2002).

Cd absorption in animals fed either SFK or rice was not affected by marginal dietary Zn unless both Fe and Ca were also marginal. Marginal Fe, on the other hand, enhanced Cd absorption by 50 to 60% in diets with either food component. Marginal dietary Ca had a similar effect. In rats fed the 40% rice diets, marginal intakes of Fe and Ca combined caused a 6-fold increase in Cd absorption over that in animals consuming adequate intakes of these minerals. In addition, rats fed the rice-based diet with marginal Fe and Ca absorbed significantly more Cd than rats fed the SFK-based diet with a marginal supply of these minerals (Fig. 1).

In these and subsequent studies, it was found that marginal Zn, Fe, and/or Ca status seemed to correlate with a slower transit time of Cd through the gut of rats. The fecal excretion of a dose of ^{109}Cd incorporated into the food was delayed in those marginally deficient in Fe and Ca, when compared to rats with adequate mineral status (Reeves and Chaney, 2001; Reeves and Chaney, 2002). In rats receiving adequate Fe and Ca, up to 90% of the unabsorbed ^{109}Cd was excreted in the feces over the first 4 days after dosing. However, during the same period, only about 60% was excreted in rats fed the marginal diet (data not shown). When Zn was marginal as well, the delay in Cd excretion was even more pronounced. Importantly, these diets contained Cd concentrations that occur in natural foods (0.25–0.45 mg/kg), not toxicological concentrations as used in most studies of this nature.

To determine whether marginal mineral status affected gut retention of dietary Cd, studies were performed to monitor the changes in Cd concentrations of the gut enterocytes over time. Rats were fed the 40% rice diet as described above, except that only groups adequate or marginal in all three minerals; Zn, Fe,
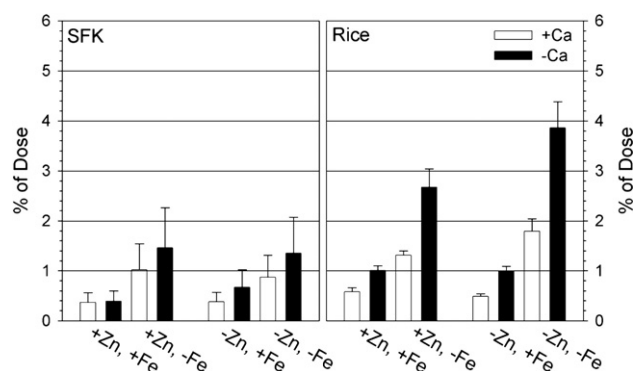

Fig. 1 – Whole body retention of ^{109}Cd is affected by mineral nutrient status of rats. Female rats were fed diets containing either 20% ground sunflower kernels or 40% cooked dried rice, each containing 0.25 mg Cd/kg. Each diet also contained marginal or adequate amounts of Zn, Fe, or Ca. After 5 weeks, each rat was given 1.0 g of diet labeled with ^{109}Cd. After 16 days, the amount of label remaining in the body was monitored and expressed as a percentage of the initial dose. Values are means ± SEM for eight replicates. Graph reconstructed from data in Reeves and Chaney (2001, 2002).
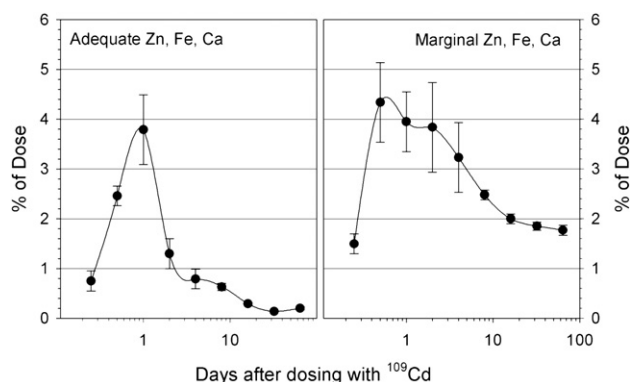
Fig. 2 – Retention of an oral dose of [109]Cd is affected by the mineral nutrient status of rats. Female rats were fed rice-based diets marginally deficient in Zn, Fe, and Ca for 5 weeks and then given 1.0 g of diet labeled with [109]Cd. The amount of label remaining the body minus intestine was monitored over the next 64 days and expressed as the percentage of the initial dose. Values are means±SEM for six replicates. Graph reconstructed from data in Reeves and Chaney (2004).

and Ca, were studied. Again, the dietary Cd concentration in this experiment was kept near that normally found in foods that contain a natural abundance of Cd. The rats consumed their respective diets for five weeks and then each received 1.0 g of diet labeled with [109]Cd. At 0.25, 0.5, 1, 2, 4, 8, 16, 32, and 64 days after dosing, six rats from each group were anesthetized and killed by exsanguinations. The intestine from each rat was removed and divided into five sections, beginning with the first 10 cm of the duodenum, then 20 cm segments thereafter. Each segment was analyzed for [109]Cd and Cd. After the intestine was removed, each animal was assayed for [109]Cd content by whole-body counting. Liver and kidneys were then removed and analyzed for [109]Cd and Cd.

By counting the whole-body without the intestine, it was found that rats fed either the marginal or the adequate Zn, Fe, Ca diets retained similar amounts of the label between days 0.5 and 1.0 (Fig. 2). However, between days 1 and 64, less [109]Cd was lost in rats fed the marginal diet than in those fed adequate diets. At day 64, the marginal diet group retained about 2% of the label while the group fed the adequate diet retained only 0.2%. Although rats fed both the adequate and marginal diets consumed similar amount of Cd, rats fed the marginal diet absorbed more Cd and lost it more slowly than rats fed the adequate diet. This suggests that the turnover rate of Cd in the body of rats fed the marginal diets was less than that in rats fed the adequate diets.

The enterocytes of rats fed marginal concentrations of Zn, Fe, and Ca took up about 40% of the [109]Cd in the first 24 h after dosing (Fig. 3). In the same period, the amount of label transferred to the rest of the body was only about 4% (Fig. 2). Duodenal enterocytes of the adequately fed rats took up only 20% as much [109]Cd as the enterocytes of the marginally fed rats (Fig. 3); however, the amount transferred to the body was similar to that of the marginally fed rats (Fig. 2). This suggests that the mechanism of Cd release from duodenal cell to the blood was not affected as greatly by the marginal deficiency as was the uptake mechanism at their apical surface. The biological half-life of [109]Cd in the duodenum of marginally fed rats was twice that of rats fed adequate diets; 1.1 days vs. 0.5 days (Reeves and Chaney, 2004). Other segments of the intestine retained much less Cd than the duodenum. The first segment of the jejunum in the marginal rats, for example, retained only about 12% as much label as the duodenum. Over time, the amount of label in each segment decreased to very low concentrations.

The Cd concentrations in the intestinal segments also were affected by the mineral nutrient status of the rats (Fig. 4). The concentration of Cd in the duodena of rats fed the marginal mineral diet was as much as 10 times higher than that in the
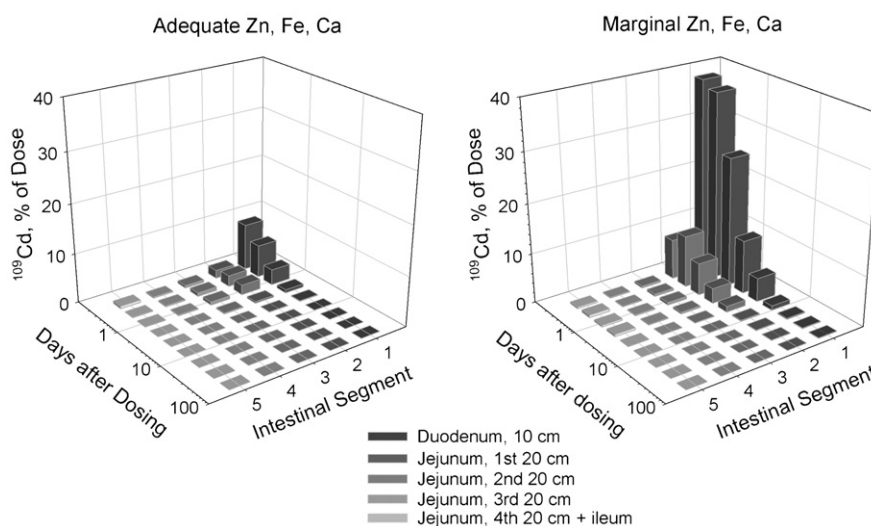

Fig. 3 – Marginal mineral status affects the retention of an oral dose of [109]Cd in intestinal segments of rats fed rice-based diets. Female rats were made marginally deficient in Zn, Fe, and Ca for 5 weeks and then given 1.0 g diet labeled with [109]Cd. At intervals over the next 64 days, the intestines were removed and divided into segments. The amount of label remaining in each intestinal segment was monitored with a gamma counter and expressed as the percentage of the initial dose. Values are means±SEM for six replicates. Graph reconstructed from data in Reeves and Chaney (2004).
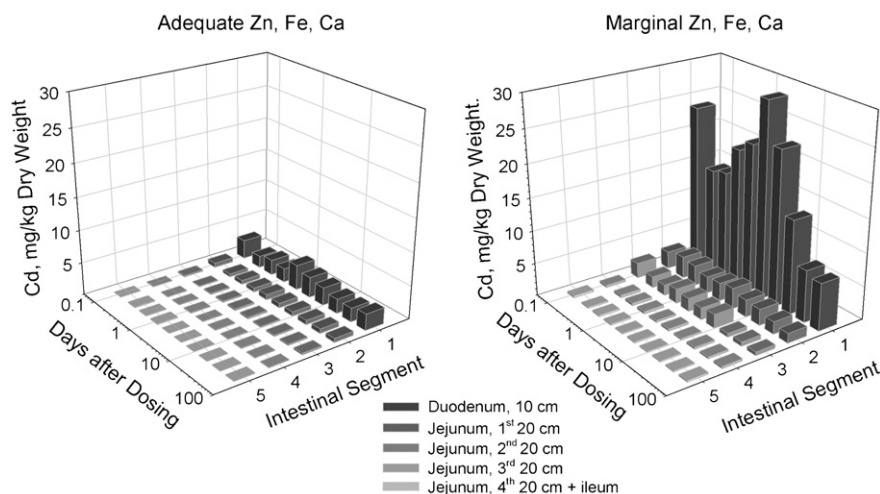
Fig. 4 – Marginal mineral status affects the retention of Cd in intestinal segments of rats. Female rats were fed rice-based diets marginally deficient in Zn, Fe, and Ca for 5 weeks. At intervals over the next 64 days, the intestines were removed and divided into segments. The concentration of Cd in each intestinal segment was measured by furnace atomic absorption spectrometry and expressed as mg Cd/kg dry weight. Values are means ± SEM for six replicates. Graph reconstructed from data in Reeves and Chaney (2004).

rats fed adequate minerals, but the values were variable. From day 4 to day 64, the concentration seemed to decrease; but we have no explanation for this phenomenon given that the rats received similar amounts of dietary Cd throughout the experiment. The amount of Cd in the other segments was very low compared with that in the duodenum. This suggests that animals fed very low amounts of Cd in the diet accumulate most of it in the duodenum, and the Cd is not recycled to other parts of the intestine. As the duodenal cells are sloughed off, the Cd is passed out of the gut; however, as the animals continuously consume the low Cd diet, the next generation of enterocytes accumulates similar amounts of Cd. This is in contrast with Cd accumulation in the intestine of rats fed high amounts of dietary Cd. Elsenhans et al. (1994) fed rats 220 mg Cd/L of water for 8 days and found higher Cd in the distal jejunum than in any other segment. It is likely that the high Cd intake saturated the Cd binding sites in the duodenum and the excess unbound Cd was able to migrate farther down the tract where it was taken up by the jejunal enterocytes.

As discussed above, Cd is readily taken up by the duodenal enterocytes, but its transfer into the blood is inefficient. Recent evidence suggests that Cd is taken up via the intestinal Fe transporter, DMT1 (divalent metal transporter-1), which is located in the apical membrane of the enterocytes (Park et al., 2002; Bannon et al., 2003). It has been shown that the DMT1 is most active in the duodenum at around pH 5.5, which is the pH near that of the luminal fluid of the proximal duodenum. The high activity of DMT1 could be part of the explanation for a higher concentration of Cd in this intestinal segment than in other parts of the intestine. Both DMT1 protein concentration and the gut lumen concentration ratio of Cd:Fe are up-regulated during low Fe status (Fleming et al., 1999; Park et al., 2002; Ryu et al., 2004). As a result, Cd is transported into the enterocytes at an enhanced rate; thus, increasing the potential for more Cd to be exported to the circulation. Ryu et al. (2004) showed that the message for the transporter, ferroportin 1

(FPN1), that moves Fe out of the enterocyte was up-regulated by Fe deficiency, and this was correlated with an increased concentration of Cd in various organs. However, direct evidence that FPN1 is the primary means of Cd transfer from the enterocyte into the circulation has not been reported. A recent curious finding by Öhrvik et al. (2007) showed no negative correlation between Fe status and Cd uptake in the gut of suckling piglets. In fact, the higher the Fe status, the higher the rate of Cd uptake. In addition, Suzuki et al. (2008) found normal uptake of Cd in anemic mk/mk mice, suggesting that DMT1 transporter was not totally responsible for Cd uptake in the intestine. This is borne out in our studies (Reeves and Chaney, 2004) as well as those of Kello et al. (1979) and Saric et al. (2002) suggesting that the Ca transport mechanism might be associated with Cd absorption.

Because high Cd intakes induce intestinal metallothionein (MT), which binds Cd, an increase in MT has been considered a likely storage form of Cd. Thus, for some time, it had been proposed that induced MT was responsible for the higher concentrations of Cd in the intestine of rats consuming marginal amounts of Ca, Fe, and Zn. However, recent studies by Reeves et al. (2005) showed that this is not the case. The study used MT-null mice that do not produce intestinal MT. It was shown that these mice fed diets marginally deficient in Ca, Fe, and Zn accumulated Cd in the intestine to the same extent as mice with normal MT production. This suggests the presence of another intestinal component besides MT that binds Cd.

Because of the decreased turnover rate and increased organ retention, more Cd is retained by various organs of rats fed marginal diets, compared with those from rats fed adequate diets. For example, the amount of [109]Cd transferred to the liver and kidneys was much greater in the marginal than the adequate group (Fig. 5). For illustrative purposes, the values are expressed on a linear (upper part of Fig. 5) and a $\log_{10}$ (lower part of figure) scale for days after dosing. Liver
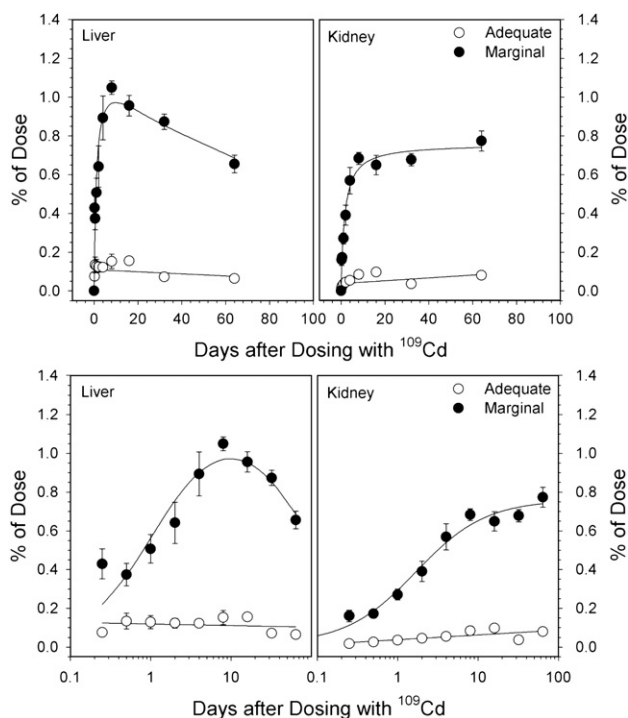
Fig. 5 – Marginal mineral status affects the retention of an oral dose of [109]Cd in liver and kidney of rats. Female rats were fed rice-based diets marginally deficient in Zn, Fe, and Ca for 5 weeks and then given 1.0 g diet labeled with [109]Cd. At intervals over the next 64 days, the liver and kidneys were removed and analyzed for [109]Cd with a gamma counter and expressed as a percentage of the initial dose in the whole organ. Values are means ± SEM for six replicates. Graph reconstructed from data in Reeves and Chaney (2004).

[109]Cd gradually increased with time, peaked at 8 days after dosing, but then began to diminish. Kidney, on the other hand, maintained an elevated amount of the label throughout the 64-day experimental period. In addition, the concentrations of Cd in the liver and kidneys were higher in the marginally fed rats than in the adequately fed ones (Fig. 6).

3. Implications for risk assessment of Cd toxicity during mineral malnutrition

Questions remain about risks from Cd in foods and in contaminated soils. We have been investigating the possible risk of rice diets containing Cd concentrations similar to that consumed by subsistence rice farmers. Historically, farmers who consumed rice grown in fields flooded with water contaminated with Cd and Zn from mine wastes are the only human populations known to have been harmed by dietary Cd (Chaney et al., 1999). Soils with geogenic sources of Zn and Cd contain about 200-times more Zn than Cd, but rice grown in these soils does not have an increased grain Zn, even though there is a large increase in grain Cd. Increased rice grain Cd also occurs even in flooded soils with much higher ratios of Zn to Cd (Chaney et al., 2001; Simmons et al., 2003). We know of no crops other than rice that accumulate more Cd out of proportion to Zn in the edible tissues when grown on geogenic Zn/Cd contaminated soils (Chaney et al., 1987).

Poor nutritional quality of polished rice with respect to Zn and Fe is of world-wide concern (Graham et al., 1999; Gregorio et al., 2000; Welch and Graham, 2002; Graham et al., 2007). Anemia and low Zn status are rampant in populations subsisting on rice (Fortes et al., 1998; Shankar and Prasad, 1998; Ross, 2002). The World Health Organization has estimated that malnutrition as a result of vitamin A, Zn, and Fe deficiencies causes a large percentage of deaths in children under the age of five (Black, 2003). This problem is so severe that an international program was established by the Consultative Group on International Agricultural Research (CGIAR) Centers to breed rice and other staple foods with higher densities of bio-available Fe and Zn than presently available (Gregorio et al., 2000; Graham et al., 2001; Gregorio, 2002). Thus, it is reasonable to suggest that a close connection exists between the consumption of low Zn/Fe-high Cd rice-based diets and food-chain Cd disease in long-term residents of Zn/Cd contaminated areas of the world.

Rice-based diets seem to have a unique association with Cd disease. For example, diets that contain shellfish may have high concentrations of Cd, but are not as clearly associated
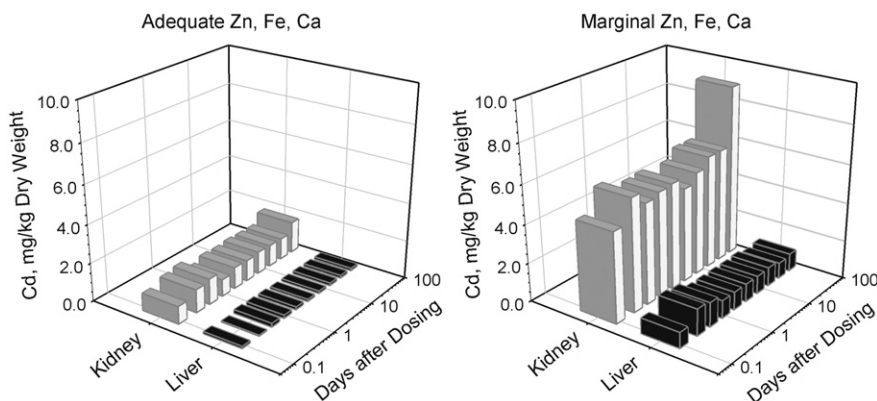

Fig. 6 – Marginal mineral status affects the retention of Cd in liver and kidney of rats. Female rats were fed rice-based diets marginally deficient in Zn, Fe, and Ca for 5 weeks. At intervals over the next 64 days, the liver and kidneys were removed and analyzed for Cd by furnace atomic absorption spectrometry and expressed as mg Cd/kg dry weight of tissue. Values are means ± SEM for six replicates. Graph reconstructed from data in Reeves and Chaney (2004).

with Cd disease in humans. McKenzie-Parnell et al. (1987, 1988) found no adverse effects in individuals who consumed large numbers of Cd-rich oysters. Likewise, Vahter et al. (1996) found no increase in blood Cd in young women who regularly consumed shellfish that added nearly three times as much Cd to their intake as women who did not consume shellfish. It was significant that they found higher serum ferritin concentrations in the shellfish consumers than in the control group (Vahter et al., 1996). Perhaps the consumption of the Zn/Fe-rich oysters elevated their Fe status and reduced their absorption of Cd.

Our recent work might help explain why rice has been a central player in the high incidence of proximal renal tubular Cd disease in human. Because no other dietary exposure to a Cd source has regularly caused Cd disease, it seems that there is a sensitizing factor in the rice-consuming populations, or that the bioavailability of Cd in rice is different from other foods. Combining our findings with the possible Zn/Fe malnutrition found in subsistence rice consumers suggests that the absorptive transport mechanisms for Zn and Fe, especially Fe, are up-regulated in these individuals, which in turn facilitates the absorption of Cd. Thus, because rice excludes Zn and accumulates Cd into grain, and is inherently low in Fe, rice could have a unique ability to increase Cd uptake and to slow Cd turnover in the small intestine. The slower turnover rate of Cd would increase the likelihood of Cd entering the circulation rather than being rapidly eliminated in the stool as seen in animals with adequate Fe and Zn nutriture.

It is of interest to note that renal tubular dysfunction has not been observed in populations consuming garden foods or other crops grown on Cd contaminated soils over long periods [Shipham, UK, (Strehlow and Barltrop, 1988); Palmerton, PA, USA, (Sarasua et al., 1995); Stolberg, Germany, (Ewers et al., 1993)]. This is remarkable because these garden soils contained 10-fold higher Cd concentrations than the rice soils in Japan and China where kidney tubular dysfunction was prevalent. This may indicate that the European and American inhabitants consumed a variety of garden foods that accumulated Zn, Fe, and Ca along with Cd, and gave them a higher mineral intake that would have reduced the absorption of Cd.

4.   Conclusions

From these findings, it seems likely that bioavailability plays a major role in the assessment of the risk of food Cd and in the management of that risk. If findings from large-scale human studies prove to be similar to our current studies with rats, then it seems clear that populations with marginal to low Zn, Fe, or Ca status could be susceptible to food Cd poisoning as seen in Japan and China. Some reports have already shown that humans who have low Fe status are likely to absorb more Cd than those with adequate Fe status. It is recognized that a marginal nutrient status induced in the consumer who subsists on rice-based diets could cause a much greater absorption of Cd than occurs with other staple diets. Thus, this suggests that nutritional supplementation could diminish the risk to individuals that are likely to be harmed by soil/food contamination with Cd. A Zn–Fe–Ca supplement, or a balanced vitamin–mineral supplement appropriate for their

diets, would maintain the small intestine in a state that would discourage efficient Cd absorption, and would allow the enterocyte Cd to be excreted soon after ingestion.

These findings also have implications for the design of food safety rules for Cd. Because the dietary source plays such a significant role in the risk of Cd from rice, it seems evident that different foods would require different Cd limits. There is no technical basis, for example, to extrapolate the limit of 0.4 mg/kg for Cd in rice to that of wheat or other foods. Furthermore, although most soil Cd contaminations are geogenic with 200-times more Zn than Cd, some industrial contaminations result from specific addition of Cd to the soil. For example, Cd is used without Zn in Cd–Ni batteries, paint pigments, plastic stabilizers, and electroplating solutions. Without concurrent addition of Zn, the potential for soil Cd transfer to foods is much greater, and Cd bioavailability to animals and humans might be even more pronounced.

Lastly, we would like to stress the importance of food-level exposures of Cd and other potentially toxic elements in the study of risk assessment. Most foods contain low concentrations of Cd that are poorly absorbed, except for rice-Cd; consequently, it is neither relevant nor practical to use toxic doses of Cd in experimental diets to study food Cd risks. In addition, the metabolic processes that seem to allow rice to induce the absorption of Cd in humans have not been observed in most other Cd exposures. Therefore, a more comprehensive understanding of the biochemistry involved in the bioavailability of Cd from a variety of foods would help resolve remaining questions and provide the support for a badly needed food safety policy regarding food Cd.

Acknowledgements

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